Summary of Safety and Effectiveness

I. General Information

A. Device Generic Name:	Fluorescence System
B. Device Trade Name:	Karl Storz Autofluorescence System
C. Applicant's Name and Address:	Karl Storz Endoscopy-America, Inc. 600 Corporate Pointe Culver City, CA 90230
D. Premarket Approval Application (PMA) Number	P020008
E. Date of Panel Recommendations	none
F. Date of Notice of Approval to the Applicant	December 12, 2002

II. Indications for Use

The Karl Storz Autofluorescence system is indicated for use in white light and autofluorescence bronchoscopy to identify and locate abnormal bronchial tissue for biopsy and histological evaluation. It is indicated in patients who:

- are suspected of having broncho genic carcinoma and are scheduled for a bronchoscopy as part of a standard diagnostic staging or work-up
- have been previously diagnosed with lung cancer and who are at high risk for recurrence
- have abnormal sputum cytology
- have abnormal chest X-ray, CT scan or similar technology

III. Contraindications

For both white light (WL) and autofluorescence (AF) examination:

- patients with uncontrolled angina, uncontrolled heart failure, or serious uncontrolled ventricular arrhythmias
- patients with uncontrolled hypertension
- patients with a white blood cell count less than 2,000 or greater than 20,000 and/or a platelet count less than 50,000
- patients with a known bleeding disorder or who are on anticoagulant therapy

For AF examination:

- patients who have received photosensitizing agents (hematoporphyrin derivatives) within three months prior to the procedure
- patients who are on, or have received, chemopreventive (e.g., retinoic acid) agents within 3 months prior to the procedure
- patients who have received ionizing radiation treatment within 3 months prior to the procedure
- patients who have received systemic cytotoxic chemotherapy within 4 months prior to the procedure

IV. Warnings and Precautions

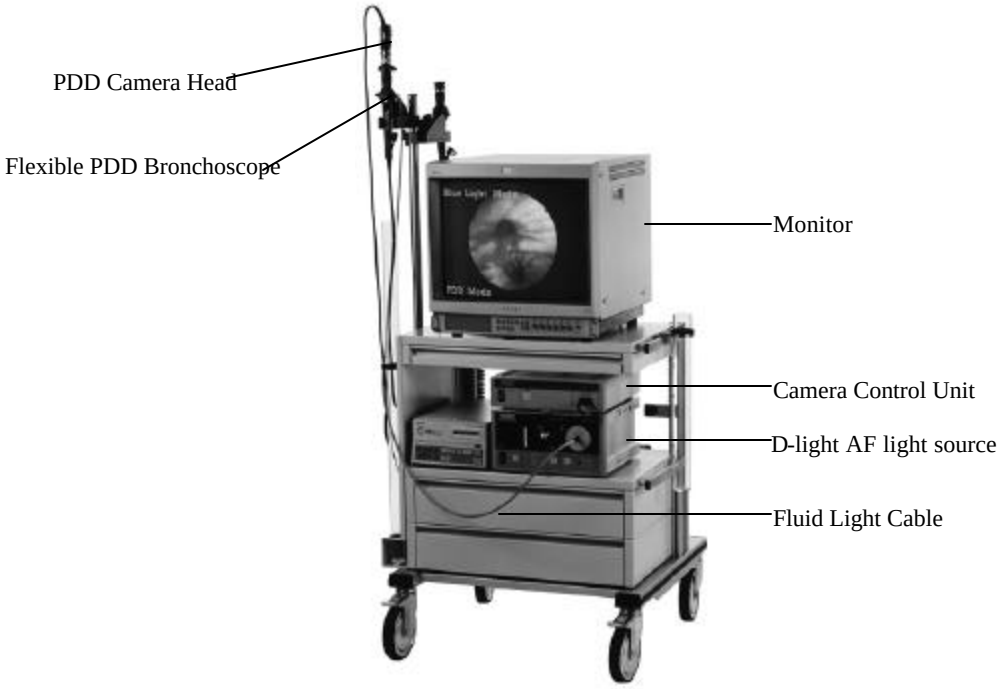
The warnings and precautions can be found in Karl Storz Autofluorescence System labeling.

Safety and effectiveness of the device was not evaluated in patients younger than 18 years. The risks and benefits are not expected to be different than those in the adult population. The physician is advised to use caution in patients less than 18 years.

V. Device Description

The Karl Storz Autofluorescence System is a fluorescence system intended for use in white light and autofluorescence bronchoscopy to identify and locate abnormal bronchial tissue for biopsy and histological evaluation. The Karl Storz Autofluorescence (AF) System consists of a light source for diagnosis (D-light AF), a flexible PDD bronchoscope, fluid light cables, and a PDD camera system (Telecam® /Tricam® SL PDD).

The D-light AF light source connects to the flexible PDD bronchoscope by use of the fluid light cable. The light source is also connected to the camera system by use of an accessory cable. The PDD camera head is coupled to the eyepiece of the PDD bronchoscope so that the image can be viewed on a monitor. Light from the D-light AF light source is focused through the fluid light cable connected to the bronchoscope and carries light through the scope to illuminate the area to be observed. The image is transmitted from the bronchoscope's distal tip to the eyepiece/PDD camera head coupling and displayed on a monitor connected to the camera system. Once the D-light AF is connected to the camera system by the accessory cable, the PDD camera head is automatically synchronized to control the light modes of the D-light AF light source.



The Karl Storz AF System is designed to induce and view tissue autofluorescence. The D-light AF emits light in either the entire visible spectrum, i.e., WL mode (390 to 770 nm) or the blue portion, i.e., AF mode (380 to 440 nm), of the visible spectrum. Blue light is used to excite naturally occurring molecules in the mucosa of the tracheobronchial tree. Excitation of these molecules causes fluorescent light to be produced resulting in the phenomenon known as tissue autofluorescence. Tissue autofluorescence may be viewed using an emission or observation filter that restricts the light to the appropriate wavelengths. The Karl Storz flexible PDD bronchoscope includes an emission filter that is integrated into the eyepiece specifically for viewing of tissue autofluorescence, which can be observed in the green to red portion of the visible spectrum (475 - 800 nm). Tissue autofluorescence can be viewed either directly through the eyepiece of the PDD bronchoscope or on a video monitor using the respective PDD camera head attached to the eyepiece of the PDD bronchoscope.

The D-light AF light source is a 300 watt short arc xenon light source with two modes of operation, the white light (WL) mode and the autofluorescence (AF) mode. When the D-light source is turned on, it automatically defaults to the WL mode. In the WL mode, light from the entire visible spectrum is emitted from the light source; this mode may be used for standard WL or fiberoptic bronchoscopy.

The D-light AF light source may be switched to the AF mode by pressing the mode button on the front panel of the light source, or, when the camera is connected, a button on the camera head. In the AF mode, a filter that restricts the transmission of light to wavelengths between 380 and 440 nm, is rotated into the path of the light. These wavelengths are in the near ultraviolet (UV) to the blue portion of the spectrum, and produce broad band excitation of several naturally occurring molecules present in

the mucosa of the tracheobronchial tree. The D-light source contains optics, which focus the light into a fluid light guide that has been optimized for transmission of blue light.

The light guide is connected to the Karl Storz flexible AF bronchoscope and is designed to be used in conjunction with the D-light AF light source. The bronchoscope contains a filter wheel in the eyepiece with two positions, one for the autofluorescence (AF) mode and one for the white light (WL) mode. When the filter is in the AF position, emission of light is restricted to wavelengths in the range of 475 to 800 nm, which is the optimal range for detection and viewing of tissue autofluorescence. The WL position on the bronchoscope filter wheel contains no filter and allows transmission of white light in the visible range (390 to 770 nm) for standard white light bronchoscopy.

Typically, molecules responsible for tissue autofluorescence are excited by light in the range of 380 to 440 nm (the AF mode of the D-light source), and will emit fluorescence which is detectable at 510 - 520 nm (within the range of the AF position of the bronchoscope filter wheel). The combination of the excitation filter in the D-light source (380 - 440 nm) and the emission filter in the bronchoscope (475 - 800 nm) optimizes the contrast, increases the illumination, and allows visualization of instrumentation while the system is in the AF mode.

In addition to the filter wheel, the Karl Storz flexible AF bronchoscope features an instrument channel for passage of biopsy forceps or other instruments, and a suction channel for removal of fluid. A disposable suction valve is a required accessory. It is packaged sterile, single use and is cleared through the premarket notification process. The bronchoscopes' diameters range from 5.0 mm to 6.4 mm, with instrument channels of 2.3 mm to 2.8 mm. The distal tip of the flexible bronchoscope can be deflected 180^{o} upward and 100^{o} downward.

The Karl Storz PDD camera systems (Telecam® or Tricam®) are compact CCD cameras that may be attached to the eyepiece of the flexible PDD bronchoscope. The AF system may be integrated via coupling with the Karl Storz PDD camera head. The PDD camera system is designed to communicate with the light source and synchronize the illumination and detection modes of the D-light AF light source and the camera. When the PDD camera is attached, the D-light AF light source modes may be controlled by the buttons on the PDD camera head.

The PDD camera system contains an optimized optical system and an image processing module (IPM) that allows the image to be integrated for 1/15 of a second to increase the sensitivity of the fluorescence detection. The AF mode of the camera also features a specially adapted color balancing function for optimal viewing of fluorescent images. The use of the PDD camera system allows the procedure to be viewed on a monitor or to be videotaped without loss of the fluorescence signal.

VI. Alternative Practices and Procedures

Alternative tests used to detect and diagnose lung cancer include tests such as chest X-rays, sputum cytology, CT scans, PET scans, MRI, transbronchial needle aspiration, mediastinoscopy and thoracotomy.

VII. Marketing History

The Karl Storz Autofluorescence System has been marketed in Europe, Eastern Europe, the Middle East, Asia, Japan, Australia, Canada, and South America. The Karl Storz Autofluorescence System received a CE mark in June 1993 and was first distributed in 1998. The Autofluorescence System has not been withdrawn from marketing for any reason relating to its safety or effectiveness.

VIII. Adverse Effects of the Device on Health

The most common side effects experienced by patients in this study were sore or hoarse throat (10% of population) and bloody sputum (8.3%). A portion of the population (3-4%) also experienced cough, shortness of breath (dyspnea), and bleeding. Other adverse effects reported with less frequency during the clinical evaluation of the device were those normally associated with standard bronchoscopic procedures. They included fever, infection, arrhythmia, bronchospasm, laryngospasm, chest discomfort, hypersensitive reaction to medications, hypoxemia, hypoxia, nausea or vomiting, pneumothorax, and irregular blood pressure. Potential adverse effects may include bacteremia and hypoventilation which are sometimes associated with bronchoscopy.

Additional biopsies may be taken as a result of enhanced detection of suspicious lesions by the autofluorescence examination. The risks of complications from endobronchial biopsies are lower than the risks from transbronchial biopsies. These risks have been estimated to be approximately 1%. The risks are lower since the tissue is visible during the endobronchial procedure and the bronchial wall is not traversed.

The length of the bronchoscopic examination will be longer than it is for standard bronchoscopy if the white light and autofluorescence examinations are combined. The probability of experiencing an adverse effect while using the Autofluorescence System may be increased by the additional biopsies and longer examination time associated with the use the combined use of WL and AF modes. However, all adverse effects experienced should be similar to those of white light bronchoscopy.

Tissue and DNA damage by the blue light range of the AF mode of the Autofluorescence System have also been considered. Non-clinical tests indicated that the risk of tissue damage from exposure to blue light (380 to 440

nm) from the autofluorescence exam is less than that from exposure to the white light used in a conventional fiberoptic examination. Additionally, the range of blue light radiation (380 to 440 nm) is not considered mutagenic.

IX. Summary of Preclinical Studies

Karl Storz cites conformance with the following consensus standards:

Testing/Analysis	Standard	AF System Component
Electrical Safety	UL2601-1	D-light AF Light Source and Telecam®/Tricam® camera
Current Leakage	IEC 601-2-18	Flexible PDD Bronchoscope
EMC	IEC 60601-1-2	D-light AF Light Source and Telecam®/Tricam® camera
Risk Analysis	EN 1441	Autofluorescence System
Biocompatibility	ISO 10993-1, "Biological evaluation of medical devices-Part 1: Guidance on selection of tests"	Flexible PDD Bronchoscope

Bench Testing

Bench testing included testing of general fluorescence spectroscopy systems, which assessed the safety of "blue" light exposure to tissue from various prototype systems (non-Karl Storz Endoscopy America systems). It was concluded that the relative risks of illumination using wavelengths of 337 nm, 380 nm, and 460 nm are lower or comparable to those of white light (Xenon) systems currently in use for diagnostic procedures, such as colposcopy. Bench testing on the excitation and blocking filters incorporated into the D-light AF and the emission filter incorporated into the flexible PDD bronchoscope was also performed to ensure that all of the filters in the AF System performed according to manufacturing specifications.

The optical resolution, electrical safety, and thermal safety of the PDD bronchoscope were tested both before and after ethylene oxide sterilization cycles and soak/disinfection cycles. The results of the testing demonstrated the continued reliability and durability of the bronchoscope. Bench testing performed on the PDD camera systems tested the camera control unit (CCU)

processor, the PDD camera head and the correct alignment and connection of CCU and camera head. The results indicated that they conformed to the product specifications and validated the system design.

Radiant Exposure

Testing was conducted to compare the energy emitted from the WL mode and the AF mode of the D-light AF unit. Energy output in mW and visible light output in lumens were measured using appropriate equipment. The spectral irradiance or flux density of the integrated excitation waveband for the AF mode and the full spectrum for the WL mode were measured using a spectroradiometer and a calibrated receptor. The testing was performed at various distances from a surface, as would be typical when using a bronchoscope in clinical practice. The results of the testing indicated that the irradiance emitted by the AF mode (380 to 440 nm) was slightly more than that emitted by the WL mode (390 to 770 nm). This slight increase would not be expected to result in tissue damage.

Electrical/EMC Testing

The D-Light AF light source and PDD camera systems were tested for electrical safety and were shown to comply with the UL2601-1 standard. Electrical isolation testing was done on the eyepiece of the PDD bronchoscope, which is the part of the scope in closest contact to the physician's face. The eyepiece was demonstrated to be both electrically and thermally insulating. The instrument channel is also manufactured from an electrically non-conductive material. Additionally, current leakage testing was performed on the PDD bronchoscope per IEC 601-2-18 protocol. The initial measurement of current leakage did not differ after a light source was introduced to the scope.

Electromagnetic compatibility (EMC) testing for emissions, immunity, electrostatic discharge (ESD), radiated RF electromagnetic fields, bursts, and surges performed on the D-Light AF unit and PDD camera systems demonstrated that they both complied with the IEC 60601-1-2 standard. No EMC testing was necessary for the PDD bronchoscope since there are no electrical connections integrated into the scope. The bronchoscope is fully insulated.

Engineering Testing

Quality testing of the engineering of the PDD bronchoscope included testing of the optical resolution, environment effects on optical performance, electrical safety, mechanics, and thermal safety. The testing results indicated that the bronchoscope was engineered according to product specifications. Similar engineering testing of the D-light AF unit included testing of the software compliance with good software development practices, operational readiness in

a simulated real environment, correctness of the compilation and burning procedures, and correct functionality of the displays and indicators on the faceplate, as well as the controls (e.g., light output pushbutton switches and light mode pushbutton switch). Testing was also done to ensure that there was sufficient quality assurance in place to meet product specifications, electrical safety and electromagnetic compatibility.

Validation testing was done to ensure that the engineering of the PDD camera system conformed to product specifications. Testing included electrical safety, AGC range, electromagnetic compatibility, environmental effects on the device, resolution, shutter speeds, signal to noise ratio, and software functions. Additional engineering testing on the PDD camera heads included imaging, minimum and maximum illumination, pixels, focal length and range, video signal system and head electronics.

Failure Mode Effects Analysis (FEMA)/Hazard Analysis

The risk analysis for the Karl Storz AF System consisted of the identification of potential hazards, an assessment of the level of risk they posed, and proposals of solutions to mitigate these risks. A risk value number was assigned to each identified hazard, and failure mode and effect analysis was used in the risk analysis process. The functions with the highest risk value included insufficient light for the AF mode, incorrect shutter speed, use of an incorrect light source or light cable, improper color balancing, improper selection of light mode and dysynchronization of light modes between D-light and camera. A solution for each of these identified risks was provided.

The risk level of the AF System is not any greater than that of any general bronchoscopy procedure. The greatest risk to a patient using the Autofluorescence System is the potential for a wrong diagnosis. Since all diagnoses are confirmed by pathology, it is unlikely that a patient will be incorrectly diagnosed solely by the AF System. The risk analysis of the light source and camera system were also reported based on EN 1441. The risks relating to both devices have been considered and all possible hazards have been mitigated to the lowest degree of risk level.

Software Testing

Karl Storz Endoscopy America, Inc. and its subsidiaries, utilized a detailed process in the development of the software elements of the Autofluorescence System. The process consisted of a comprehensive schema used to create, test, revise and document the software and/or firmware employed in the AF System. Through this process, Karl Storz carefully controlled each aspect of the development of the code, beginning with the drafting of functional requirements and specifications through the design of the code, maintaining and documenting revisions, planning and conducting software and firmware design verification testing and, finally, validating and certifying the readiness of the software and hardware production. Only the D-light AF light source and PDD camera systems contain a software element.

Stress Testing/Life Testing

Stress and wear testing performed on the bronchoscope included passing a working instrument through the working channel of the bronchoscope many times. This was done in the non-deflected position and repeated with the scope deflected in both directions. The working channel was then examined for internal abrasion, kinks and bond joint condition, and no damage to the inside wall was evident.

Stress and wear testing of the D-light AF unit consisted of a lamp performance comparison between the light output of a PDD lamp and standard 300W Xenon lamp. The degradation curves of both lamps conformed to the same pattern over time and showed that the PDD lamp consistently generated more light energy output than the standard 300W lamp in compliance with the product specifications.

Biocompatibility Testing

The direct patient contact portions of the KSEA Autofluorescence System are the flexible PDD bronchoscope shaft and its distal tip. Both the shaft and the distal tip of the PDD bronchoscope meet the ISO 10993-1 standard for biocompatibility. All biocompatibility tests were performed according to the FDA Good Laboratory Practice (GLP) regulations, 21 CFR, Part 58. The tests performed included an irritation test of intracutaneous reactivity, sensitization (guinea-pig maximization test), and cytotoxicity testing using the ISO elution method. Additional tests conducted followed USP guidelines and included mutagenicity testing, a systemic injection test, and an intracutaneous injection test. The testing results on the materials were all within acceptable parameters for biocompatibility.

Sterilization

All components of the Karl Storz Autofluorescence System are reusable except for the sterile, single-use disposable suction valve, a required accessory. Suction valves are provided with the bronchoscope when purchased and are available for purchase as a separate item. The PDD bronchoscope is provided to the customer in a non-sterile condition. Prior to use, the PDD bronchoscope must be sterilized by the user with ethylene oxide (ETO) gas, which has been validated by the AAMI overkill method to an SAL = 10^{-6}. The flexible PDD bronchoscope can also be chemically disinfected using a high-level disinfecting solution containing a 2% concentration of glutaraldehyde. The suction valves (11301 CE) will be sold sterile and will be single-use devices. Sterilization of the D-light AF is not necessary or required. The casing can be wiped with a damp cloth and germicide. The PDD camera heads can be disinfected with standard 2% glutaraldehyde solutions or sterilized by the STERIS® System 1 Processor, STERRAD 100 System, or ethylene oxide method. The camera control units may be wiped with a damp cloth and germicide, if needed.

X. Clinical Investigations

A. Pilot Study

A pilot study using the Karl Storz AF System was conducted in Gauting, Germany at the Clinic for Pneumology. The study was conducted following Good Clinical Practice Guidelines and the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained from all patients who participated in the study. A total of 64 subjects were examined with the Karl Storz AF System.

Results of Karl Storz AF System Pilot Study (Gauting, Germany)

Sixty-four subjects were examined with both WL and AF and 264 biopsies were obtained. The results of this study indicate that for identification of dysplasia and carcinoma *in situ* (Class III), the AF mode was more sensitive (83%) than the WL mode (33%). However, when used to identify visible tumors (Class IV), the AF mode and the WL mode were equally sensitive. The specificity of the AF mode was slightly less (89%) than that of the WL mode (94%) for Class III lesions. Therefore, there was a slightly increased risk of taking a biopsy from normal tissue that may appear abnormal using the AF mode.

B. IDE Clinical Study

Study Objectives

The primary objectives of the study were to evaluate the safety and effectiveness of bronchoscopy with the Karl Storz AF System in the AF mode as compared to the WL mode for the visual detection of Class III bronchial lesions (defined as moderate/severe dysplasia, carcinoma *in situ*, microinvasive carcinoma, or early invasive carcinoma), in patients with known or suspected lung cancer, or with completely resected Stage I/II lung cancer with no evidence of metastatic disease.

Safety was evaluated by the number and severity of the adverse events related to use of the device. Effectiveness was evaluated by comparing the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of bronchoscopy in the AF mode compared to the WL mode.

The study hypothesis was that there is at least a 20% difference in sensitivity between bronchoscopy in the autofluorescence (AF) mode versus bronchoscopy in the white light (WL) mode of the AF system, for the detection of Class III bronchial lesions.

There were six investigational sites included in the clinical trial. All six institutions were within the United States.

Study Design

The AF System study was a prospective, non-randomized, single-blind (pathologist evaluating biopsies was blinded with respect to the results of the WL and AF bronchoscopic examinations), multi-center clinical study of a diagnostic device in clinical practice. Each patient received a bronchoscopic examination using the AF System in the WL mode followed by a second examination in the AF mode. All endoscopic examinations were videotaped.

All tissue was classified as either “normal” (Class I/II), “abnormal/pre - malignant changes” (Class III), or “tumor” (Class IV) as shown in Table I below.

Table 1. Description of Visual Tissue Classification

Visual classification	Short Description	Histopathological Description
Class I	Normal	Normal epithelium with no visible lesion
Class II	Normal/non-specific changes	Normal epithelium with inflammation, trauma, metaplasia, hyperplasia, or mild dysplasia
Class III	Abnormal/ premalignant changes	Moderate/severe dysplasia, carcinoma *in situ*, microinvasive carcinoma, invasive carcinoma
Class IV	Visible tumor	squamous carcinoma/adenocarcinoma

All visible areas that were classified as Class III (in either WL or AF mode) were biopsied for histological evaluation to determine sensitivity, positive predictive value, and negative predictive value. Class IV biopsies were taken at the discretion of the investigator. A minimum of two random (2) biopsies were required from areas classified as "Class I - normal" in **both** the WL mode and the AF mode to determine sensitivity, specificity, and negative predictive value.

Biopsies were reviewed by a pathologist at the clinical trial site and subsequently sent to an independent reference pathologist for evaluation. Both the local site pathologist and reference pathologist were blinded to the biopsies' visual classification. Only the results issued by the reference pathologist were considered as the final pathological diagnosis and used to determine study endpoints.

Histopathological Codes

The reference pathologist used the following standardized histopathological rating codes (Table 2) to classify each biopsy received. Class IV denoted a biopsy that was unsatisfactory for various reasons (e.g. insufficient tissue for histological diagnosis):

Table 2. Histopathology Codes

Code	Visual Classification	Histopathological Classification
1	Class I/II	Normal/Nonspecific changes defined as: • Normal tissue • Inflammation, Metaplasia, Hyperplasia, Mild Atypia /Dysplasia
2	Class III	Abnormal/premalignant changes defined as: • Moderate Atypia (Dysplasia), Severe Atypia (Dysplasia), Carcinoma *in situ*, Microinvasive carcinoma, Invasive carcinoma
3	Class IV	Tumor
4	Unsatisfactory	Unsatisfactory

Study Population

It was determined that, based on worst-case scenario projections for the distribution of the data, a sample size of 300 patients would be necessary in order to generate 195 positive (Class III) biopsies.

A total of 195 positive biopsies was derived to provide at least 80% power to detect a minimum of 20% difference in sensitivity between WL and AF for the detection of bronchial lesions that fit the criteria of moderate/ severe dysplasia, carcinoma *in situ*, microinvasive carcinoma, or invasive carcinoma (or Class III) using a 2-tailed McNemar test declaring the 5% alpha level to be statistically significant, and the following assumptions:

- An average of 4 biopsies per patient will be obtained (aside from mandatory Class I biopsies)
- Minimal patients will be lost to follow-up
- Approximately 90% of the biopsies will be evaluable
- At least one positive biopsy will be obtained from approximately 70% of the study population.

However, the 300 patients enrolled yielded a total of only 85 "positive" biopsies as determined by histological examination. The minimum difference of 20% was nonetheless detected without a total of 195 lesions since WL only detected a total of 9 positive lesions while AF detected 52.

- Most of the patients in the study population were smokers (> 90%)

- Study enrollment included 180 men (60%) and 120 women (40%)
- The study patients ranged in age from 38 to 88 years, with a median age of 66 years
- Most of the study patients were Caucasian in ethnicity (82.3%)
- A segment of the study population had a history of significant respiratory disease (67%)
- A small portion had prior lung cancer history (15%)

Study Period

The length of the study participation per subject was determined by the number and frequency of the intervention(s). The screening visit occurred as early as 30 days prior to the bronchoscopy. The second visit included the bronchoscopy and biopsy retrieval. A follow-up visit was completed 5 to 14 days after the procedure.

Inclusion and Exclusion Criteria

Inclusion Criteria

- male and non-pregnant female patients 18 years of age or older
- patients with known or suspected bronchogenic carcinoma, based on a history of symptoms, who were scheduled for a bronchoscopy as part of a standard diagnostic or staging work-up.
- patients with completely resected Stage I/II lung cancer with no evidence of metastatic disease who were at high risk for lung cancer recurrence (non-metastatic)

Exclusion Criteria

- patients with uncontrolled angina, uncontrolled heart failure, or serious uncontrolled ventricular arrhythmias
- patients with uncontrolled hypertension
- patients with known bleeding disorders or who use anticoagulants
- patients with white blood cell counts < 2,000 or > 20,000 and/or platelet counts < 50,000
- patients who were allergic to local anesthetic agents
- patients who had received photosensitizing agents within 90 days of the procedure
- patients who were on, or had received, chemopreventive agents within 90 days of the procedure
- patients who had received ionizing radiation to the chest within 3 months of the procedure
- patients who had received cytotoxic chemotherapy systematically within 4 months of the procedure

Clinical Trial Sites and Investigators

There were six U.S. investigational sites included in the IDE clinical trial.

- Indiana University Medical Center - Francis Sheski, M.D., Principle Investigator
- Beth Israel Deaconess Medical Center - Armin Esnst, M.D., Principle Investigator
- Lahey Clinic Medical Center - John Beamis, M.D., Principle Investigator
- Henry Ford Hospital - Michael Simoff, M.D., Principle Investigator
- Johns Hopkins Hospital - Edward Haponik, M.D., Principle Investigator
- Los Angeles County USC Medical Center - David Gelmont, M.D., Principle Investigator

The designated reference pathologist was Dr. Friolan Espinoza, of Quest Diagnostics in San Juan Capistrano, California.

Summary of Clinical Studies

A. Safety Evaluation

Clinical safety of the Autofluorescence System was assessed through a review of the adverse events that occurred during the clinical trial. A total of 300 patients and 901 biopsies were considered in the clinical safety analysis.

The most common side effects experienced by patients were hoarseness or sore throat (10% of population) and bloody sputum (8.3%). A portion of the population (3-4%) also experienced cough, shortness of breath (dyspnea), and bleeding. Other adverse effects reported with less frequency during the clinical evaluation of the device were those normally associated with standard bronchoscopic procedures. They included fever, infection, arrhythmia, bronchospasm, laryngospasm, chest discomfort, hypersensitive reaction to medications, hypoxemia, hypoxia, nausea or vomiting, pneumothorax, and irregular blood pressure. None of the side effects that occurred were directly attributable to the autofluorescence mode of the device but were expected side effects of any bronchoscopic procedure.

B. Effectiveness Evaluation

Effectiveness was assessed by comparing the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the WL examination to that of the AF examination in identifying lesions which require biopsy for histological evaluation. Because the AF mode is indicated as an adjunct to the WL mode, the performance of the combined modalities (AF+WL) was also assessed. Both visual detection modes were compared to the histology of the tissue (gold standard) in terms of their ability to locate

precancerous lesions defined as moderate to severe dysplasia, carcinoma *in situ,* microinvasive carcinoma, and early invasive carcinoma.

The effectiveness evaluation utilized biopsies as the unit of analysis as the biopsies were considered to be independent experimental units. A total of 901 biopsy results were retrieved from the 300 patients enrolled in the AF System study. However, the current analyses use a dataset of 821 biopsy observations from 293 patients. Three biopsy observations had missing pathology information as the biopsies did not survive initial processing at the local site pathology lab. An additional 77 biopsies were either tumors by visual or histopathological examination (34) or rated as unsatisfactory specimens (43) by the reference laboratory. Thus, a total of 80 (8.8%) biopsy observations out of 901 were omitted. An average of 2.8 biopsy observations were retrieved per person.

The visual tissue classifications were collapsed into two groups. Biopsies visually classified as Class I and Class II were collapsed into the bronchoscopically negative group; biopsies visually classified as Class III were placed into the bronchoscopically positive group. Histologically positive biopsies were defined as biopsies identified as being moderate to severe dysplasia, carcinoma *in situ,* microinvasive carcinoma, or early invasive carcinoma.

Table 3. Summary of Biopsy Data

		Biopsy Result	
		+	-
WL	+	TP = 9	FP = 40
	-	FN = 76	TN = 696
Total		85	736

AF	+	TP = 52	FP = 182
	-	FN = 33	TN = 554
Total		85	736

TP = true positive, FP = false positive, FN = false negative, TN = true negative

As shown in Table 3, of the 821 evaluable biopsies derived from the study population, 85 were rated as histologically positive. An approximately six-fold increase in the detection of true positive biopsies with AF compared to WL was also accompanied by an approximately 4.5 fold increase in false positive biopsies.

The biopsy-based sensitivity of the AF mode to detect histologically positive biopsies increased by 51% (10.6% to 61.2%) over WL (Table 4). Sensitivity of the combined modalities (WL + AF) was 65.9%. These sensitivities are likely overestimates of the true sensitivities because the nature of the study is such that their denominators were undercounted. However, the relative sensitivity, or ratio of the sensitivity of WL + AF as compared to WL alone, is unbiased and was 6.22 (95% CI: 3.15-12.31). The false positive ratio of WL + AF versus WL is also unbiased as was 5.03 (95% CI: 3.56-7.09, $p<0.0001$). Please see complete data summary presented in the following table:

Table 4. Summary of Efficacy Results
(Based on 821 biopsies)

	WL	AF	WL + AF
Sensitivity	*10.6%	*61.2%	*65.9%
Specificity	*94.6%	*75.3%	*72.7%
Positive Predictive Value	18.4%	22.2%	21.8%
Negative Predictive Value	*90.2%	94.9%	94.9%
False Positive Rate	5.4%	24.7%	27.3%
Relative Sensitivity			6.22†
False Positive Ratio			5.03†

* Estimate is biased because the nature of the study precludes proper determination of its denominator.

† 95% confidence intervals were (95% CI: 3.15-12.31) for relative sensitivity and (95% CI: 3.56-7.09) for ratio of false positive rate.

The results indicate that there was a decrease in AF specificity compared to WL specificity due to an increase in the false positive rate with the AF mode when compared to the WL mode.

When Class IV biopsies or tumors are included in the analysis, the number of biopsies positive for moderate/severe dysplasia or worse (including visible tumors) increases to 114 out of a total of 855 biopsies. The sensitivity of WL versus AF to detect moderate/severe dysplasia or worse is 28.1% versus 66.7%. The combined modalities (WL+AF) provide a 71.9% sensitivity rate to detect abnormal areas and tumor lesions (relative sensitivity compared to WL was 2.56). Please see results with tumors included in Table 5 below.

Table 5. Efficacy Results – Tumor biopsies included

(based on 855 biopsies)

	WL	AF	WL + AF
Sensitivity	*28.1%	*66.7%	*71.9%
Specificity	*93.9%	*74.9%	*72.2%
Positive Predictive Value	41.6%	29.0%	28.5%
Negative Predictive Value	*89.5%	*93.6%	94.4%
False Positive Rate	6.1%	25.1%	27.8%
Relative Sensitivity			2.56†
False Positive Ratio			4.56†

* Estimate is biased because the nature of the study precludes proper determination of its denominator.

† 95% confidence intervals were (95% CI: 1.9-3.45, $p<0.0001$) for relative sensitivity and (95% CI: 3.31-6.33, $p<0.0001$) for ratio of false positive rate.

The results indicate that there was a decrease in AF specificity compared to WL specificity due to an increase in the false positive rate found with the AF mode when compared to the WL mode.

Gender-Based Analysis

Sensitivity of the Autofluorescence System was 58.2% in males and 66.7% in females. While the sensitivity was slightly higher in females, there was no statistically significant difference between the gender-based cohorts, indicating that the AF System was equally effective for both gender groups.

Age-Based Analysis

Median age in the study population was 66 years, consistent with the lung cancer prevalence data from the American Cancer Society. Patients were stratified for analysis by less than 66 years of age and greater than age 66. Sensitivity and specificity estimates were better in biopsies obtained from patients over age 66.

Risk/Benefit Analysis

There is some degree of risk of experiencing an adverse effect while using the AF System due to the additional bronchoscopy time required by using the AF mode and the additional biopsies obtained. However, the adverse effects that occurred during the clinical evaluation of the device were not directly attributable to the AF System. In general, the adverse effects were similar to those that would have occurred with any bronchoscopic procedure. This increased risk is balanced by the increase in sensitivity of the AF mode (61.2%) over the WL mode (10.4%) to detect biopsies displaying moderate to severe dysplasia, carcinoma *in situ*, microinvasive carcinoma, and early invasive carcinoma.

Device Failures

The AF System components include the D-light AF light source, the flexible PDD bronchoscope, fluid light cables, and a PDD camera system. The incidences of device component malfunctions were recorded during the clinical trial and are discussed below.

Three patient procedures were aborted during the trial due to device component failures or misuse. No patient injuries occurred due to these malfunctions.

- In one procedure, the fluid light cable malfunctioned and the procedure was aborted.
- During device testing prior to a procedure, the D-light AF light source would not produce light due to a failure of its internal power supply. The scheduled procedure was aborted and the site was sent a replacement unit.
- At one site, the user was unable to switch the system correctly to the AF mode to continue the AF exam and biopsy procedure. The site was provided with additional technical training on the AF system, and this problem did not recur.

Device Component Replacements

A. Flexible PDD Bronchoscopes

Bronchoscopes were replaced during the conduct of the AF clinical trial when they became damaged. Sites were immediately provided with working replacements; the damaged scopes were evaluated for failure causality and subsequently repaired.

Seven bronchoscopes were found to have leaks in their distal covers. Improper cleaning and sterilization methods used by site staff damaged five bronchoscopes. One site accidentally closed the case on the shaft of a bronchoscope and left it damaged. The deflection component of three bronchoscopes required adjustment, and three additional bronchoscopes were replaced due to a damaged image bundle, a damaged light guide, and a detached lens, respectively.

B. D-light AF light sources

Two additional instances of D-light AF malfunctions were reported. None of the malfunctions occurred during a procedure but were discovered during system testing prior to the procedure. In one case, the unit's internal power supply failed and was replaced. No problem was found with the second unit and the reported problem could not be duplicated. However, in the interest of ensuring optimal performance, the unit's internal power supply was recalibrated.

C. PDD Camera Systems

One site reported a PDD camera system malfunction. No problem was found with the component; however, the camera system was recalibrated to ensure optimal performance.

XI Panel Recommendations

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act or 1990, this PMA was not referred to the Ear, Nose and Throat Panel, an advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII CDRH Decision

The clinical investigations conducted with the Karl Storz Autofluorescence System, used as an adjunct to white light bronchoscopy, showed that the AF mode of the Autofluorescence System can enhance the physician's ability to detect and locate abnormal bronchial tissue suspicious for moderate to severe dysplasia, carcinoma *in situ*, microinvasive carcinoma, and early invasive carcinoma, for biopsy and histological evaluation, when compared to the WL mode. The device has been demonstrated to be safe and effective when used an indicated.

The manufacturing facilities were inspected and found to be in compliance with Quality System Regulations.

CDRH issued the approval order on December 12, 2002.